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(54) Title: DENTAL FORMULATION

(57) Abstract

This invention concerns inhibiting tooth enamel demineralization by using a water soluble phosphate, particularly a pyrophosphate or tripolyphosphate, to inhibit demineralization while not negatively impacting remineralization.

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Dental Formulation

Area of the Invention

This invention concerns inhibiting tooth enamel demineralization. More specifically it relates to the use of a water soluble phosphate, particularly a pyrophosphate or tripolyphosphate, to inhibit demineralization while not negatively impacting remineralization. This provides a means for preventing or reducing dental caries.

Much work has been done to reduce tooth decay by chemical means. Decay has a number of causes. One most commonly thought of is enamel demineralization. The most widely used approach to preventing demineralization and to remineralize enamel is to present a fluoride ion to the oral cavity via a mouthwash or other short term topical application means. Fluoridated drinking water has had a material impact in reducing dental caries. Other approaches use dentifrices, pastes applied directly to the teeth by professionals, or oral rinses which contain a fluoride ion as a means for fluoridating teeth. Dentifrices, pastes and mouthwashes contain a low level of a fluoride salt, most often as the alkali metal fluorides, alkali metal salts of monofluorophosphate and stannous fluoride. A usual, and effective, fluoride concentration in these types of products is on the order of 1100 parts per million (ppm). To date no other chemical approach has been developed as a means for inhibiting enamel demineralization and thus preventing or treating dental caries.

It has been found that certain water soluble phosphates exemplified by the alkali metal pyrophosphates and tripolyphosphates inhibit demineralization of enamel and they do not interfere with the remineralization phenomena of the fluoride ion in subsurface caries-like lesions. This finding makes it possible to provide an anti-caries dental preparation which does not use fluoride.

Summary of the Invention

This invention has two aspects. One is a method for reducing or preventing dental caries in humans by inhibiting enamel demineralization, which method comprises treating the teeth with a formulation containing a demineralization inhibitor consisting essentially of an effective non-toxic amount of a water soluble pyrophosphate or tripolyphosphate in an orally acceptable carrier. In the second aspect, this invention covers an orally acceptable formulation

for preventing dental caries in humans by reducing or preventing demineralization which comprises an orally acceptable carrier and an inhibitor of enamel demineralization consisting essentially of an effective non-toxic amount of a water soluble pyrophosphate or tripolyphosphate.

Specific Embodiments

In the broadest embodiment, this invention utilizes certain phosphates as a means for inhibiting tooth enamel demineralization and thus reducing or preventing dental caries. It has been found that the presence of a orally acceptable water soluble phosphate is the critical factor, not the acid or salt form in which it is presented. Such a phosphate may be an orthophosphate, a pyrophosphate, a polyphosphate (chain phosphates) or a metaphosphate (cyclic phosphates). The preferred phosphates are pyrophosphate and tripolyposphate. So far as the ionic form of the phosphate is concerned, the acid form of each of these phosphates should not be used. That is acid phosphates such as $H_5P_3O_{10}$ or $H_4P_2O_7$ should not be used. But the partially neutralized forms may be used, though the fully neutralized forms are usually preferred. The salts of Group Ia alkali metals of periods 2, 3 and 4 are preferred, particularly the sodium and potassium forms and mixtures thereof. Most preferred is $Na_5P_3O_{10}$ alone or mixtures of $Na_4P_2O_7$ and $K_4P_2O_7$. Notwithstanding this preference, several phosphate types and ionic forms may be incorporated into a single preparation. The phosphate may be anhydrous or hydrated.

Many commercial sources sell suitable phosphate preparations. In particular sodium and potassium pyrophosphate and sodium tripolyphosphate are available from a number of companies. Or the salts may be custom prepared to define standards by a commercial source or by the one who is doing the formulation work by using published techniques and processes. Pure phosphate preparations meeting local regulatory requirements should be used in these dental preparations.

Effective concentrations of phosphate will vary with the type of phosphate selected, its water solubility, the type of product (i.e., toothpastes, mouthwashes, chewing gums) and may be influenced by the nature and chemical or physical characteristics of the carrier and co-formulated excipients. Some ingredients or formulations may have a higher available phosphate content. In any event, an effective amount is that amount which will reduce enamel demineralization to an extent

that dental caries will be reduced in a statistically significant manner over a phosphate-free control which is also free of any other demineralization inhibiting agent or remineralizing agent.

As a practical matter, though not intending to be bound by such lower limit, about 2% by weight, or more, of a phosphate ion should provide an effective anti-caries preparation when used incorporated into orally acceptable preparations and when used in a normal, routine fashion. A preferred baseline for toothpastes, gels and liquids is 5% by weight. As regards sodium tripolyphosphate concentrations, 5% w/w is a preferred amount. As for pyrophosphates, a preferred amount is about 1.8% tetrasodium pryophosphate and 4.0% tetrapotassium pyrophosphate. These amounts, when combined with the excipients normally used to confect pastes and gels, should provide sufficient available phosphate to inhibit enamel demineralization to a point where dental caries will be usefully reduced. Variations and refinements in the level of phosphates can be carried out as required or as appropriate to maximize the effectiveness of the phosphate in a given formulation. Phosphates may represent a higher percentage of the overall ingredient profile in dry formulations such as dental tablets, lozenges and chewing gums.

These phosphates can be presented in any orally acceptable carrier. The only limitation is that the phosphate must be available to interact with tooth enamel and the formulation must not have any deleterious or untoward affects on the teeth or the oral cavity when used within approved guidelines.

Many orally acceptable formulations are known in the dental arts. Broadly speaking, these include dentifrices (pastes, gels and liquids), tooth powders, mouth rinses, dental tablets, dental lozenges, and dental care chewing gums, for example. Three of the most preferred formulations are toothpastes, gels, and mouthwashes. These will be specifically illustrated below as of orally acceptable formulations contemplated in the use of this invention.

Toothpastes, gels and liquid formulations may be prepared with conventional ingredients, keeping in mind that certain abrasives may not be compatible with certain water soluble phosphates. These potential limitations are detailed below. Aside from this one limitation, one can use pretty much any combination of dentally acceptable

abrasive, humectant, detergent, sweetening agent, flavor, antimicrobial agent, coloring agent and pigment and the like. A preferred toothpaste or gel will contain about 5% of the pyrophosphate salt or tripolyphosphate salt, about 10 to 80% of a humectant, about 0.25 to 5% of a detergent, up to 2% sweetening and flavoring agents (in combination), coloring agents, binders and thickening agents, and water in amounts sufficient to make a stable, flowable paste or gel.

The abrasive polishing material contemplated for use in the present invention can be any material which does not excessively abrade dentin. These include, for example, silicas including gels and precipitates, calcium pyrophosphate, calcium polymetaphosphate, insoluble sodium polymetaphosphate, hydrated alumina, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and others such as disclosed by in U.S. Pat. No. 3,070,510 incorporated herein by reference. Mixtures of abrasives may also be used. Certain abrasives may not be compatible with the metioned phosphates. For example calcium carbonate, dicalcium orthophosphate dihydrate, and tricalcium phosphate are best avoided if the maximum effect of the water soluble phosphates are to be realized.

Silica dental abrasives, of various types, can provide the unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentin. Silica abrasive materials are also exceptionally compatible with many ionic materials including the phosphates which are the subject of this invention. For these reasons they are preferred for use herein.

The silica abrasive polishing materials useful herein, as well as the other abrasives, generally have an average particle size ranging between about 0.1 and 30 microns, preferably 5 and 15 microns. The silica abrasive can be precipitated silica or silica gels such as the silica, xerogels described in U.S. Pat. No. 3,538,230 and U.S. Pat. No. 3,862,207, both incorporated herein by reference. Preferred are the silica xerogels marketed under the trade name "Syloid" by the W.R. Grace & Company, Davison Chemical Division. Preferred precipitated silica materials include those marketed by the J.M. Huber Corporation under the trade name, "Zeodent." These silica abrasives are described in U.S. Pat. No. 4,340,583, incorporated herein by reference.

The abrasive in the dentifrice compositions described herein is present at a level of from about 6% to about 70%, preferably from about 15% to about 25% when the dentifrice is a toothpaste. Higher levels, as high as 90%, may be used if the composition is a tooth powder.

Flavoring agents can also be added to the dentifrice and other compositions of the present invention. Suitable flavoring agents include oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, and oil of clove. Sweetening agents are also useful and include aspartame, acesulfame, saccharin, dextrose, levulose and sodium cyclamate. Flavoring and sweetening agents are generally used in the compositions herein at levels of from about 0.005% to about 2% by weight.

The dentifrice compositions of this invention, may also contain emulsifying agents. Suitable emulsifying agents are those which are reasonably stable and foam throughout a wide pH range, including anionic, nonionic, cationic, zwitterionic and amphoteric organic synthetic detergents. Nonionic surfactants are preferred. Many of these suitable surfactants are disclosed in U.S. Pat. No. 4,051,234 incorporated herein by reference.

Water is also present in the toothpaste compositions of this invention. Water employed in the preparation of commercially suitable compositions should preferably be deionized and free of organic impurities. Water generally comprises from about 10% to 70%, preferably from about 20% to 40%, by weight of a toothpaste. These amounts of water include the free water which is added plus that which is introduced with other materials such as when sorbitol or other polyhydric alcohols which are manufactured as dilutions where water is the diluent.

Thickening agents generally are added to toothpastes and gels to provide a desirable consistency. Preferred thickening agents are carboxyvinyl polymers, carrageenan, hydroxyethyl cellulose and water soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as gum karaya, gum Arabic, and gum tragacanth and polysaccharide gums such as xanthan gum can also be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Hydroxyethyl cellulose is a

preferred binder. Thickening agents in an amount from 0.5% to 5.0% by weight of the total composition may be used.

It is also desirable to include a humectant in a toothpaste to keep it from hardening. Suitable humectants include glycerin, sorbitol, and other edible polyhydric alcohols such as PEGs, at a level of from about 10% to about 70%.

Antibacterial agents may be added to these pastes and gels (and mouthwashes). Any one of a number of antibacterial drugs or agents may be used. Triclosan, 5-chloro-2-(2,4-dichlorpphenoxy)phenol, is one example. A group of useful antibacterials is the cationic antibacterial agent. Suitable cationic antibacterial agents for use in dentifrices include:

(i) quaternary ammonium compounds, for instance those in which one or two of the subsistent on the quaternary nitrogen has between 8 and 20, preferably 10 and 18 carbon atoms and is preferably an alkyl group, which may optionally be interrupted by an amine, ester, oxygen, sulphur, or heterocyclic ring. The remaining nitrogen substituents will have a lower number of carbon atoms, for instance between 1 and 7, and are preferably alkyl, for instance methyl or ethyl, or benzyl. The anion will be an orally acceptable salt forming group. Examples of such compounds include benzalkonium chloride, dodceyl trimethyl ammonium chloride, benzyl dimethyl stearyl ammonium chloride, cetyl trimethyl ammonium bromide, benzethonium chloride (diisobutyl phenoxyethoxyethyl dimethylbenzyl ammonium chloride), and methyl benzethonium chloride;

ii) pyridinium and isoquinolinium compounds, exemplified by hexadecylpyridinium chloride, cetyl pyridinium chloride, and alkyl isoquinolinium bromide;

(iii) pyrimidine derivatives such as hexetidine (5-amino-1,3-Bi(2-ethylhexyl)-5-methylhexahydropyrimidine);

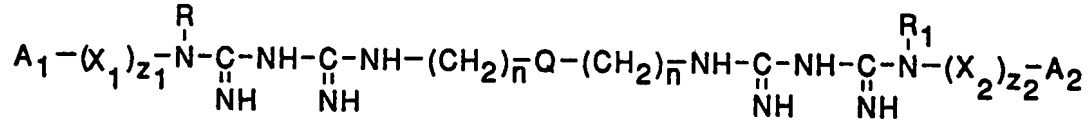
(iv) aniline derivatives such as hexamidine isothionate (4,4'-diamonding-a,w-diphenoxyhexane isothionate);

(v) bispyridine derivatives such as octenidine(N,N'[1,10-decanediyldi-1(4H)-pyridinyl-4-ylidine]bis(1-octanamine dihydrochloride); and

(vi) biguanides including:

(a) mono-biguanides such as *p*-chlorobenzyl biguanide and N'-(4-chlorobenzyl)-N"-(2,4-dichlorobenzyl)biguanide.

(b) bis-biguanides of the general formula (I):



(I)

wherein:

A_1 and A_2 are independently a phenyl group optionally substituted by (C_{1-4})alkyl, (C_{1-4})alkoxy, nitro, halogen, $C_{1-12})$alkyl group, or (C_{4-12})alicylclic;

X_1 and X_2 are independently (C_{1-3})alkylene;

R and R^1 are independently hydrogen, (C_{1-12})alkyl, or aryl(C_{1-6})alkyl;

Z_1 and Z_2 are independently 0 or 1;

Q is CH_2, oxygen, sulfur, or aryl;

n in each $(CH_2)_n$ group is independently an integer from 1 to 12 but the total of both n groups may not exceed 12;

aryl is phenyl, naphthyl or another aromatic ring; and orally acceptable acid addition salts thereof. Preferred compounds are chlorhexidine and alexidine.

(c) poly(biguanides) such as polyhexamethylene biguanide hydrochloride.

An effective amount of a antibacterial agent is in the range of about 0.005 to 10% weight/weight (w/w), preferably 0.005 to 5%, more preferably 0.005 to 2.5% and most preferably 1.0% w/w.

An optional ingredient which may be useful in any of the present compositions which contains a cationic antimicrobial agent is an anti-stain agent. Cationic antimicrobial materials may cause staining when used at fairly high levels. Anti-stain agents include carboxylic acids such as those disclosed in U.S. Pat. No. 4,256,731, incorporated herein by reference. Other agents include amino carboxylate compounds as disclosed in U.S. Pat. No. 3,937,807; dicarboxylic acid esters as disclosed in U.S. Pat. No. 4,080,441; and phosphonoacetic acid as disclosed in U.S. Pat. No. 4,118,474. All of these patents are also incorporated herein by reference.

Conventional manufacturing techniques can be used in mixing pastes and for filling them into flexible or solid tube-type containers, or any other convenient container form, for consumer use. There are no container limitations, so far as is known, for any form of toothpaste or gel prepared in accordance with this invention. A toothpaste of the present invention may be prepared in a uniform color or in the form of a striped toothpaste. A suitable apparatus for filling toothpaste tubes with striped toothpaste is described in U.K. Patent Specification No. 962,757.

Conventional mouthwashs can be prepared with the phosphates of this invention. Mouthwashes generally comprise about 20:1 to about 2:1 of a water/ethyl alcohol solution and preferably other ingredients such as flavoring agents, sweeteners, humectants and surfactants. Suitable flavoring agents include oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, and oil of clove. Sweetening agents which can be used include aspartame, acesulfame, saccharin, dextrose, levulose and sodium cyclamate. Suitable humectants include sorbitol and glycerin while suitable surfactants include oleate and laurate esters of sorbitol and its anhydride condensed with ethylene oxide as well as ethylene oxide and propylene oxide condensates.

Another type of surfactant which may be used are the amphoterics. The amphoteric sudsing agents useful in the present invention can be broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be straight chain or branched and wherein one of the aliphatic substituents contains from about 8 to about 18 carbon atoms and one contains an anionic water-solubilizing group, e.g., carboxylate, sulfonate, sulfate, phosphate, or phosphonate.

Generally, on a weight basis, the mouthwashes of the invention comprise 0.5% to 5% of the phosphate, 5% to 30% (preferably 5% to 20%) ethyl alcohol, 0% to 25% (preferably 3% to 20%) of a humectant, 0% to 25% (preferably 0.01% to 2.0%) surfactant, 0% to 5% (preferably 0.005% to 0.3%) sweetening agent, 0% to 0.3% (preferably 0.03% to 0.3%) flavoring agent, about 0.1% of a preservative, pH adjusting agent as needed, and the balance water.

The pH of a mouthwash and/or its pH in the mouth can be any pH which is safe for the mouth's hard and soft tissues. Generally the pH

will be adjusted to about 3 to about 10, preferably from about 4 to about 8.

Conventional manufacturing techniques and packaging materials can be used for these mouthwashes.

Other vehicles include lozenges and chewing gums. Components useful in such compositions are disclosed in U.S. Pat. No. 4,083,955, incorporated herein by reference.

Products which employee these phosphates are to be used in a conventional manner. For example, brushing the teeth with a toothpaste containing such a water soluble phosphate makes the phosphate available to the teeth and thus inhibits the formation of dental caries or reduces the development of dental caries in persons susceptible to the formation of dental caries. Mouthwashes are also used in the normal and accepted fashion to prevent caries in susceptible persons or to prevent further development of dental caries in susceptible persons Likewise dental powders, tablets, lozenges and dental care chewing gums will be used in the normal fashion and with regularity, if the effect is to be realized to its fullest degree.

The present invention is illustrated in terms of its preferred embodiments in the following Examples. All parts and percentages are by weight, based on the total weight of the product, unless otherwise stated. These Examples are given to illustrate the invention, not to limit its scope in any manner or fashion. Reference is made to the claims for determining what is reserved to the inventors hereunder.

Examples

Example 1

Toothpaste Formulation

A toothpaste can be prepared using the following ingredients and two different phosphates.

Table 1 - Tube Formulations

Ingredient	% W/W (tripolyphos)	% W/W (pyrophos)
PEG-8, FCC (PEG 400)	3.00	3.00
Xanthan Gum	0.700	0.6000
Sorbitol USP (70%)	29.9322	28.4761
Hydrated silicia (Zeofree 153)	8.000	7.000
Hydrated silicia (Zeofree 113)	14.000	14.000
Sodium tripolyphosphate	5.000	

Sodium pyrophosphate		1.810
Ptassium pyrophosphate		4.000
Sodium Hydroxide (50% solution)		0.900
Glycerin	10.000	10.000
Flavor	0.800	0.800
Sodium lauryl sulfate	1.150	1.150
Sodium saccharin	0.214	0.214
D&C Red # 30 Aluminum lake	0.025	0.025
FD&C Blue #1 (0.2%)	0.2478	0.2478
D&C Yellow #10 (0.2%)	0.2015	0.2015
Titanium dioxide	0.7235	0.7235
Sodium benzoate	0.100	0.100
Deionized water	qs 100.00%	qs 100.00%

In these two formulations, PEG-8 is a polyethylene glycol. It, along with the sorbitol and glycerin, is a humectant. Xanthan gum and the Zeofree 153 are binders and thickening agents. Three dyes are recited in this formulation as it is to be presented as a tri-colored product much like that sold under the Aquafresh brand name of SmithKline Beehcam Consumer Brands.

Because of the presence of pyrophosphates and tripolyphosphates, clear gel-like formulations cannot be prepared. But one can prepare gel-like toothpastes, albeit opaque gels, by eliminating the three dyes from the foregoing formulations.

Pump dispensers have gained favor with many toothpaste users. The following formulation can be used with a pump dispenser system.

Table 2 - Pump Dispenser Formulation

Ingredient	% W/W (tripolyphos)	% W/W (pyrophos)
PEG-8, FCC (PEG 400)	3.00	3.00
Xanthan Gum	0.700	0.6000
Sorbitol USP (70%)	29.609	28.253
Hydrated silicia (Zeofree 153)	8.000	7.000
Hydrated silicia (Zeofree 113)	14.000	14.000
Sodium tripolyphosphate	5.000	
Sodium pyrophosphate		1.810
Potassium pyrophosphate		4.000

Sodium Hydroxide (50% solution)		0.900
Glycerin	10.000	10.000
Flavor	0.800	0.800
Sodium lauryl sulfate	1.150	1.150
Sodium saccharin	0.214	0.214
D&C Red # 30 Aluminum lake	0.025	0.025
FD&C Blue #1 (0.2%)	0.2478	0.2478
D&C Yellow #10 (0.2%)	0.2015	0.2015
Titanium dioxide	0.9560	0.9560
Sodium benzoate	0.100	0.200
Purified Water	qs 100.00%	qs 100.00%

Example 2

Mouthwash Formulations

An anti-caries mouthwash employing the pyrophosphates of this invention is illustrated by the following formulation.

Table 3 - Pyrophosphate-containing Mouthwash

Ingredients	% W/W
Ethyl Alcohol, 190 proof	8.00
Glycerin, 99% U.S.P.	8.000
Sodium pyrophosphate	2.060
Potassium pyrophosphate	0.710
Flavor	0.200
Menthol	0.007
Cremophor RH-60	0.200
Pluronic F-108 (surfactant)	0.100
Pluronic F-127 (surfactant)	0.100
Benzoic acid	0.100
Sodium saccharin	0.060
FD&C #1 (0.2% solution)	0.140
FD&C yellow #5 (0.2% solution)	0.900
Phosphoric acid 25% solution to adjust pH	As needed
Deionized water	qs 100.00%

These ingredients, expect the phosphoric acid and a small amount of the water are mixed together, the pH is adjusted to the desired figure,

then the solution is brought to volume with water. This mouthwash may be packaged in any conventional bottle or container.

A similar mouthwash, but using a tripolyphosphate, is prepared as per the following formulation.

Table 4

Tripolyphosphate-containing Mouthwash

Ingredients	% W/W
Ethyl Alcohol, 190 proof	8.00
Glycerin, 99% U.S.P.	8.000
Sodium tripolyphosphate	0.50
Flavor	0.200
Menthol	0.007
Cremophor RH-60	0.200
Pluronic F-108 (surfactant)	0.100
Pluronic F-127 (surfactant)	0.100
Benzoic acid	0.100
Sodium saccharin	0.060
FD&C #1 (0.2% solution)	0.140
FD&C yellow #5 (0.2% solution)	0.900
Phosphoric acid 25% solution to adjust pH	As needed
Deionized water	qs 100.00%

Example 3

Method for Testing the Efficacy of Phosphates

The efficacy of these phosphates was determined using the following protocol:

Dentifrices (toothpastes) were prepared in plain color-coded tubes. All had the same base to which was added a tripolyphosphate, pyrophosphate, or one of these phosphates with NaF. The control was the dentifrice base. The following table gives the concentrations of actives in each formulation.

Product Description

(Fluoride as NaF, 1100 ppm F^- where shown)

Sodium tripolyphosphate (5%) without F^-

Sodium/potassium pyrophosphate (1.8/4.0%) without F^-

Toothpaste base

Sodium tripolyphosphate with F^-

Sodium/potassium pyrophosphate with F^-

The identity of the products was withheld from the technician until all experiments were completely assessed and data assembled. All experiments were conducted with color-coded tubes and all experimental racks and tubes similarly coded to keep the operatives blind. The only partial breaking of the code was when it became necessary to instruct the operative which was the correct radiotracer to add in the "hot" experiments.

The pH cycling (demineralization/remineralization) model for the *in vitro* study of fluoride-containing products and fluoride products containing anticalculus agents was that of Featherstone et al, *Caries Res.* 1988; 22:337-341. This model has previously been shown to simulate results found by us *in vivo* around orthodontic brackets (O'Reilly and Featherstone, *Am. J. Orthod.* 1987; 92:33-40). Each test cell consisted of ten human tooth crowns which were removed from the roots, cleaned and painted with acid resistant varnish to leave test windows as described in detail previously (Featherstone et al, *Caries Res.* 1988; 22:337-341).

The study was divided into "cold" legs and "hot" legs. The "cold" legs, with no radiotracer added, were used in order to determine whether the test anticalculus agents (pyrophosphate and tripolyphosphate) individually had a detrimental outcome on the net effect of demineralization/remineralization. In this case two windows, designated "upper" (towards occlusal) and "lower" (towards cervical) were placed on the enamel surface of each tooth crown. In the "hot" legs where ^{32}P labelled potassium pyrophosphate or sodium tripolyphosphate was added, one window approximately 3 x 7 mm was placed on each test surface.

The test regimen in each 24 hour period was as follows:

1. Demineralization. Teeth were immersed individually for 6 hours daily at 37 °C in 40 mL of a buffer containing 0.075 mol/L acetate, 2.0 mmol/L $CaHPO_4$ at pH 4.3.

2. Product immersion. The crowns were removed from solution, thoroughly rinsed with double deionized water (DDW), and immersed individually in 4 mL of a 1:3 slurry of dentifrice (one of the test or placebo products, see below) in DDW, and stirred on an orbital shaker for 5 minutes. The slurries were made fresh daily within 30 minutes of immersion, and where appropriate, radiotracers were added and dispersed by vortexing. After the product immersion, the samples were again thoroughly washed in DDW and transferred to the remineralizing solution.

3. Remineralization. Each tooth was then immersed individually for 17 hours at 37 °C in 20 mL of a mineralizing solution containing 1.5 mmol/L calcium, 0.9 mmol/L phosphate, 150 mmol/L KCl (to maintain ionic strength), 20 mmol/L cacodylate to buffer to pH 7.0. This solution simulates the remineralizing phase (ten Cate and Duijsters, *Caries Res.* 1982; 16:201-210) of the caries process (by salivary minerals).

Duration of pH cycling. The above pH cycling was repeated for 3 weeks, consisting of 14 cycling days and two weekend periods in mineralizing solution. The test scheme was designed to model, a total daily demineralization challenge of 6 hours, a once per day fluoride (or non fluoride) treatment, and 17 hours daily of repair (remineralization).

Test Groups. The experiments were carried out in duplicate, one group of each pair using sodium tripolyphosphate and one using pyrophosphate salts. The groups were designed to give four "cold" legs (A_1, A_2, B_1, B_2, below) which were assessed by cross-sectional microhardness testing (see below) to determine the degree of demineralization, and four identical "hot" legs (C_1, C_2, D_1, D_2) using radiolabeled sodium tripolyphosphate or pyrophosphate salts to determine the degree of penetration of the tripolyphosphate or pyrophosphate into the enamel during treatment with and without fluoride present. A fifth "cold" leg (E below) served as the baseline control and used a placebo dentifrice with no fluoride, no tripolyphosphate, and no pyrophosphate ions.

A_1. Demineralization/remineralization cycling as above with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of a sodium tripolyphosphate/sodium fluoride dentifrice (4 mL of solution per tooth individually).

A_2. In the duplicate experiment a pyrophosphate salt/NaF dentifrice was used.

B_1. Demineralization/remineralization cycling with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of an sodium tripolyphosphate non-fluoride dentifrice (sodium tripolyphosphate present as in A but with no added sodium fluoride) (4 mL of solution per tooth individually).

B_2. In the duplicate experiment pyrophosphate salts containing dentifrice without an added fluoride ion was similarly used.

C_1. Demineralization/remineralization cycling with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of an sodium tripolyphosphate/sodium fluoride dentifrice (4 mL of solution per tooth individually). In this group the sodium tripolyphosphate slurry was labeled with ^{32}P as sodium tripolyphosphate added as a radiotracer prior to immersion of the teeth.

C_2. In the duplicate experiment pyrophosphate salts were used and similarly radiolabeled with ^{32}P as pyrophosphate salts.

D_1. Demineralization/remineralization cycling with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of sodium tripolyphosphate (as in C, but with no added sodium fluoride) dentifrice (4 mL of solution per tooth individually) and with ^{32}P labeled sodium tripolyphosphate added as described above.

D_2. In the duplicate experiment pyrophosphate salts were used, similarly radiolabeled.

E. Demineralization/remineralization cycling with 5 minutes daily immersion prior to remineralization in a 1:3 slurry of a placebo dentifrice (no added sodium fluoride, no added sodium tripolyphosphate or pyrophosphate salts, 4 mL per tooth individually).

All groups used freshly made treatment slurries daily. Demineralization and remineralization solutions were replaced weekly.

Assessment Methodology

Chemical analyses: All demineralization and remineralization solutions were analyzed for fluoride ion by specific ion electrode before

use. Each individual test tube was analyzed for F^- after 7 and 14 days of cycling. Changes in F^- solution were calculated by subtracting the starting values.

Physical analyses: Groups A_1, A_2, B_1, B_2, and E were assessed by cross-sectional microhardness profiles, as described below. The duplicate radiotracer groups (C_1, C_2, D_1, and D_2) obviously could not be assessed in this manner. They were assessed by radiotracer counting as described separately below.

At the end of the cycling period, teeth from groups A, B, and E were thoroughly rinsed in DDW, sectioned longitudinally through the center of the lesions produced, and embedded in epoxy resin with the cut face exposed as described in detail previously (ten Cate et al, *Caries Res.* 1985: 19:335-341). After serially polishing the embedded teeth, each lesion was assessed by cross-sectional microhardness, according to the published methods in the references above. Indents were commenced at 25 µm from the anatomical surface and repeated at 25 µm intervals to a depth of 300 µm, across the sectioned lesion and into the sound underlying enamel. This method has been shown to give results comparable with microradiography (White and Featherstone, *Caries Res.* 1987; 21:502-512).

The indentation lengths were converted as per our published formula to volume percent, mineral and mineral loss (ΔZ) values (µm x vol % mineral) were calculated using Simpson's rule for each profile, for each lesion on each tooth, as described previously (White and Featherstone, *Caries Res.* 1987; 21:502-512). Mean values of ΔZ for each group were calculated, and mineral loss profiles were plotted as vol % mineral vs. depth from the outer surface.

Radiotracer analyses: Teeth from groups C and D were thoroughly washed in DDW and the varnish was removed individually from each tooth by acetone. Eight stepwise abrasions were made for each sample using small preweighed circles of silicon carbide paper (600 grade) to remove layers approximately 5 µm thick. Each sample was weighed, dissolved into a scintillation cocktail and the radioactivity counted in a Searle scintillation counter.

Results for sodium tripolyphosphate and pyrophosphate salt products, with and without fluoride present, were compared. The amount of lesion formation was measured by the duplicate "cold" legs (A

and B) described above as radiotracer material cannot be used in the other laboratories.

Uptake of tripolyphosphate or pyrophosphate into caries-like lesions.

This assay assessed the amount of uptake of sodium tripolyphosphate or pyrophosphate salts into preformed caries-like lesions in human enamel *in vitro*:

Test material: Human dental enamel from molars with caries free (by stereo microscope) buccal or lingual surfaces. Teeth were cleaned and prepared as described above for the pH cycling study.

Artificial caries lesion formation: Artificial caries-like lesions were produced in one window (3 x 7 mm) on one enamel surface of molars prepared in our standard manner by immersion for 5 days in a pH 5.0 buffer (0.05 mol/L lactate), 50 percent saturated with hydroxyapatite, and with 0.2% carbopol, as per the method of White (*Caries Res.* 1987: 21:228-242). This system produced lesions approximately 100 µm deep in 5 days.

Immersion in tripolyphosphate or pyrophosphate salts: Teeth with preformed caries-like lesions were individually immersed in 20mL of a 1:3 slurry of sodium tripolyphosphate or pyrophosphate salts dentifrice with ^{32}P labeled sodium tripolyphosphate or pyrophosphate salts added at similar concentration as used in the pH cycling experiments above. Groups of 10 teeth each were used. The first group was immersed for one hour and the second group for 4 hours for each of sodium tripolyphosphate and pyrophosphate salts. At the end of the immersion period the teeth were removed, rinsed in DDW and immediately air dried. They were assessed for radiotracer uptake using the abrasion method as described above.

Table 6

Relative mineral loss, ΔZ (volume % x μm) as mean values (SD = standard deviation) for each group for upper and lower windows. Values are arranged in ascending order of ΔZ values for the upper window.

Test Group	Product Description	Mean ΔZ (vol % x μm)			
		Upper Window		Lower Window	
A_2	PPi[1] Toothpaste, with NaF[3]	292	(346)	318	(368)
A_1	STPP[2] toothpaste, with NaF	597	(425)	273	(638)
B_1	STPP without NaF	1300	(814)	1996	(834)
B_2	PPi without NaF	1399	(652)	2671	(1643)
E	Placebo, no NaF, no STPP, no PPi	3809	(584)	5069	(1092)

1 PPi means potassium pyrophosphate/sodium pyrophosphate (4.0%/1.81%)
2 STPP means sodium tripolyphosphate (5%).
3 NaF at a concentration sufficient to give 1100 ppm F^-.

Both sodium tripolyphosphate and potassium/sodium pyrophosphate mix demonstrated significant reduction in caries as compared with the placebo, and approaching that demonstrated by the combination of these phosphates and NaF.

What is claimed is:

1. A method for treating or preventing dental caries by inhibiting enamel demineralization, which method comprises treating the teeth with a formulation containing a demineralization inhibitor consisting essentially of an effective non-toxic amount of a water soluble pyrophosphate or tripolyphosphate in an orally acceptable carrier.

2. The method of claim 1 which is a toothpaste or gel.

3. The method of claim 2 where the phosphate is present in at least 2% weight/weight or greater.

4. The method of claim 3 wherein the phosphate is present in at least 5% by weight or greater.

5. The method of claim 4 wherein the phosphate is pyrophosphate in the form of an alkali metal salt.

6. The method of claim 5 wherein the formulation is a toothpaste which comprises a humectant, a thickening agent, an abrasive, a surfactant, dyes, and a preservative.

7. The method of claim 6 wherein the formulation is a toothpaste which contains 1.8 % tetrasodium pyrophosphate and 4.0% tetrapotassium pyrophosphate.

8. The method of claim 4 wherein the formulation is a toothpaste which contains at least 5% by weight of tripolyphosphate and the alkali metal cation is sodium or potassium.

9. The method of claim 8 wherein the toothpaste comprises a humectant, a thickening agent, an abrasive, tetrasodium tripolyphosphate, a surfactant, dyes, and a preservative.

10. The method of claim 1 where the formulation is a mouthwash.

11. The method of claim 10 where the mouthwash contains about 0.5 to 5% of the phosphate.

12. The method of claim 11 where the mouthwash contains a tripolyphosphate alkali metal salt.

13. The method of claim 12 where the mouthwash contains sodium tripolyphosphate in an amount of about 0.5%.

14. The method of claim 13 where the mouthwash contains a pyrophosphate alkali metal salt.

15. The method of claim 14 where said pyrophosphate is a mixture of about 2.06% sodium pyrophosphate and about 0.71% of potassium pyrophosphate.

16. An orally acceptable formulation for treating or preventing dental caries in humans by reducing or preventing demineralization which comprises an orally acceptable carrier and an inhibitor of enamel demineralization consisting essentially of an effective non-toxic amount of a water soluble pyrophosphate or tripolyphosphate.

17. The formulation of claim 16 which is a toothpaste or gel.

18. The formulation of claim 17 where the phosphate is present in at least 2% weight/weight or greater.

19. The formulation of claim 18 wherein the phosphate is pyrophosphate in the form of an alkali metal salt.

20. The formulation of claim 19 which comprises a humectant, a thickening agent, an abrasive, a surfactant, dyes, and a preservative.

21. The formulation of claim 20 which contains 1.8 % tetrasodium pyrophosphate and 4.0% tetrapotassium pyrophosphate.

22. The formulation of claim 18 where the phosphate is an alkali metal salt of pyrophosphate.

23. The formulation of claim 22 which comprises a humectant, a thickening agent, an abrasive, a surfactant, dyes, and a preservative.

24. The formulation of claim 23 which contains about 5% sodium tripolyphosphate.

25 The formulation of claim 16 which is a mouthwash.

26. The formulation of claim 25 which contains about 0.5 to 5% of the phosphate.

27. The formulation of claim 26 which contains a tripolyphosphate alkali metal salt.

28. The formulation of claim 27 which contains sodium tripolyphosphate in an amount of about 0.5%.

29. The formulation of claim 13 which contains a pyrophosphate alkali metal salt.

30. The formulation of claim 14 where said pyrophosphate is a mixture of about 2.06% sodium pyrophosphate and about 0.71% of potassium pyrophosphate.

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 7/16
US CL :424/49 424/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/49 424/52 424/57

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 2,772,203 (Salman) 27 November 1956 (col. 3, lines 56-75, col.4, lines 16-25).	16-23,25,26,29,30 1-7, 10, 11
X Y	US, A, 2,876,167 (Manahan) 03 March 1959 (col.2, lines 1-27).	16-23,25,26,29,30 1-7, 10, 11
X Y	US, A, 2,941,926 (Salzman et al.) 21 June 1960. (col.3, line 40 to col.4, line 8).	16-23,25,26,29,30 1-7, 10, 11

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 JULY 1993	23 AUG 1993

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International application No.
PCT/US93/03333

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US, A, 3,137,632 (Schiraldi) 16 June 1964 (col.1, line 63 to col.2, line 4).	16-23,26,29,30 1-7, 10, 11
X Y	US, A, 3,227,617 (Manahan et al.) 04 January 1966. (col.6, lines 20-32).	16-23,26,29,30 1-7, 10, 11
X Y	US, A, 3,634,585 (Manahan et al.) 11 January 1972. (col.5, lines 10-22).	16-23,26,29,30 1-7, 10, 11
X Y	US, A, 3,927,201 (Baines et al.) 16 December 1975. (col.2, lines 5-27).	16-23,26,29,30 1-7, 10, 11
X Y	US, A, 3,934,002 (Haefele) 20 June 1976 sodium pyrophosphate col.15, line 31 disodium tripolyphosphate col.15, line 43 mixtures of the above col.15, lines 46-47.	1-30
X Y	US, A, 4,340,583 (Wason) 20 June 1982 col.11, lines 1-47, col.16, lines 3-22, 56-58, col.17, lines 1-8.	1-30
X Y	US, A, 4,515,772 (Parran et al.) 07 May 1985 col.4, lines 25-52.	16-23, 25,26,29,30 1-7, 10, 11
X Y	US, A, 4,906,456 (Gaffar et al.) 06 March 1990.(col.5, lines 29-44).	16-23, 25,26,29,30 1-7, 10, 11